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Efficacy and safety of high-voltage pulsed radiofrequency versus standard-voltage pulsed radiofrequency for patients with neuropathic pain: protocol for a systematic review and meta-analysis

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Manuscripts

1 **Efficacy and safety of high-voltage pulsed**
2 **radiofrequency versus standard-voltage pulsed**
3 **radiofrequency for patients with neuropathic pain:**
4 **protocol for a systematic review and meta-analysis**

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21
22 **Abstract**

23 **Introduction** Pulsed radiofrequency (PRF) is commonly used for the treatment of
24 neuropathic pain (NP). However, whether increasing the output voltage of PRF can safely
25 improve the efficacy of PRF treatment remains unclear. This study aims to compare the
26 efficacy and safety of high-voltage PRF and standard-voltage PRF for the treatment of
27 patients with NP.

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6 29 **Methods and analysis** We will search PubMed/MEDLINE, EMBASE, Web of Science,
7 30 and the Cochrane Library (from the date of inception until March 15, 2022), etc. Only
8 31 randomized controlled trials (RCTs) will be included. Two reviewers (YJ and GF) will
9 32 independently complete the study screening and selection, data extraction, risk of bias
10 33 assessment, and quality of evidence assessment. The primary outcome of this meta-
11 34 analysis will be the efficiency rate in patients with NP. The secondary outcomes will
12 35 include numeric rating scale (NRS), visual analog scale (VAS) score, time to take effect,
13 36 rescue drug dosage, quality of life (QoL) using the health questionnaire (SF-36), and the
14 37 incidence of adverse events (AEs). Meta-analyses will be conducted using standard meta-
15 38 analysis software (RevMan V.5.3, The Nordic Cochrane Center, The Cochrane
16 39 Collaboration, Copenhagen, Denmark).

17 40
18 41 **Ethics and dissemination** Ethical approval was waived as our systematic review will be
19 42 based on published literature. The results of this study will be submitted to a peer-
20 43 reviewed journal.

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28 45 **PROSPERO registration number** CRD42022297804.

29 46 30 47 **Strengths and limitations of this study**

31 48 To our knowledge, this will be the first systematic review and meta-analysis to evaluate
32 49 the efficacy and safety of high-voltage PRF for the treatment of patients with NP.

33 50 Only randomized controlled trials will be included in our study to provide unbiased
34 51 information than other study designs

35 52 This study findings will provide comprehensive information for future study designs in
36 53 terms of interventional treatment of neuropathic pain.

37 54 The accuracy of the conclusions of our research may be subjected to language limitations
38 55 for only English published studies will be included.

39 56
40 57 **Key words:** high-voltage, pulsed radiofrequency, neuropathic pain, randomized
41 58 controlled trials

42 59 43 44 45 46 47 48 49 50 60 **Introduction**

51 61 Neuropathic pain (NP) is a common chronic pain condition caused by lesions or diseases
52 62 affecting the somatosensory nervous system, including trigeminal neuralgia, peripheral
53 63 nerve injury pain, painful polyneuropathy, postherpetic neuralgia, central poststroke pain

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5 64 and so on.¹ Epidemiological data have reported that the global prevalence of NP is
6
7 65 approximately 6.9% - 10%.² NP is a refractory pain syndrome with a long duration of
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9 66 occurrence, frequent recurrent attacks, and poor response to traditional analgesics. Most
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11 67 patients with NP suffer from ongoing or intermittent spontaneous pain with burning,
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13 68 pricking, and a squeezing sensation with poor quality of life (QoL).³ Therefore, finding
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15 69 an effective treatment option for NP and improving patients' QoL is of great importance.
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18 70 In recent years, pulsed radiofrequency (PRF), a new type of neuromodulation technique,
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21 71 has been successfully applied in the treatment of NP.⁴⁻⁹ Different from continuous
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23 72 radiofrequency (CRF), which produces heat by friction and vibration, leading to
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25 73 thermocoagulation, denaturation, and necrosis of the target tissue, PRF provides pulsed
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27 74 energy waves followed by a 480 ms heat dissipation interval, and the temperature does
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29 75 not exceed 42°C.^{10 11} The mechanism of PRF treatment is via the modulation of nerve
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31 76 function caused by the electric field effect rather than blocking pain signal transduction.¹²
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34 77 ¹³ Thus, PRF is a nondestructive technique that can be repeatedly applied without damage
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36 78 to nerve tissue.¹¹
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39 79 The standard proposed PRF parameters were set as an output voltage of 45 V, temperature
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41 80 of 42 °C, pulse frequency of 2 Hz, output frequency of 500 kHz, continuous current action
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43 81 of 20 ms, and intermission period of 480 ms. Recently, scholars have attempted to treat
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45 82 NP patients with high-voltage PRF. Teixeira and Sluijter first reported that high voltage
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47 83 PRF of 60 V on discogenic pain patients attained satisfactory efficacy over 3 months.¹⁴
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50 84 In 2013, Luo et al found that the postoperative numeric rating scale (NRS) was
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5 85 significantly negatively correlated with the output voltage of PRF.¹⁵ Moreover, Luo et al
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8 86 also compared the efficacy of high voltage PRF and standard voltage PRF for refractory
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11 87 neuralgia infraorbital nerve therapy, and results revealed that high voltage PRF could
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13 88 achieve higher response rates at month 1, 3 months, 6 months, and one year post-
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15 89 procedure.¹⁶ However, more patients in the high-voltage group (27%) experienced mild
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18 90 numbness postoperatively than in the standard-voltage group (13%). In addition, a
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21 91 randomized controlled trial (RCT) conducted by Wan et al showed that the scores were
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23 92 significantly lower in the high-voltage group than in the standard-voltage group at 3 and
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26 93 6 months, but with no significant difference was observed at one month after treatment.¹⁷
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29 94 In addition, Wan et al 's results revealed that the incidence of ecchymoses in the high-
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31 95 voltage group (19.2%) was higher than that in the standard-voltage group (12.1%). As a
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34 96 result, whether the efficacy of high-voltage PRF at different time points is superior to that
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36 97 of standard-voltage PRF, and whether high-voltage PRF is a safe treatment method
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39 98 requires further analysis.

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41 99 The primary objectives of this study will be to compare the efficacy and safety of high-
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44 100 voltage PRF and standard-voltage PRF for the treatment of NP at different time points
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47 101 postoperatively through a systematic review and meta-analysis of RCTs.
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51 103 **Methods**

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54 104 This protocol was developed according to the reporting guidelines of the Preferred
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57 105 Reporting Items for Systematic Reviews and Meta-Analyses Protocols (PRISMA-P)
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5 106 statement¹⁸ (**checklist in Supplement 1**). The protocol for this systematic review was
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7 107 registered in the PROSPERO database (registration number: CRD42022297804). Our
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10 108 systematic review will be conducted in accordance with the recommendations of the
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13 109 Cochrane Handbook for Systematic Reviews of Interventions.¹⁹ Any amendments made
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15 110 to this protocol and the whole review process will be updated in a timely manner on the
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18 111 PROSPERO registration and the final manuscript.
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23 113 **Criteria for considering studies for this review**

26 114 **Types of studies**

28 115 Only RCTs will be included. All studies must be published in English. Experimental
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31 116 animal studies will be excluded.
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36 118 **Participants**

38 119 Patients with NP conditions recognized and defined by the International Association for
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41 120 the Study of Pain (IASP)²⁰ will be included. NP is initiated or caused by a primary lesion
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44 121 or dysfunction of the nervous system. Studies regarding diabetic neuropathy, complex
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47 122 regional pain syndrome type I, low back pain without radicular pain, and postsurgical
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49 123 pain will be excluded.
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54 125 **Interventions and Comparators**

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57 126 We will examine trials investigating high voltage PRF treatment for patients with NP.
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5 127 The high voltage PRF treatment mode will be set as a manual pulse mode: the initial
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8 128 voltage was 40 or 45 V, and the output voltage will then be gradually increased to the
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10 129 highest voltage the patient can tolerate (temperature control below 50 °C). The
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13 130 comparator will be the standard PRF treatment.

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16 17 18 132 **Outcome measures**

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20 133 The primary outcome of this meta-analysis is the efficiency rate in patients with NP. The
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23 134 predefined time points for the efficiency rate will be 1 month, 3 months and 6 months
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26 135 after the procedure. Other time points, such as 1-year or 2-years, will also be considered.
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28 136 Treatment efficiency recurrence is defined as a pain reduction of greater than 50% after
29
30
31 137 treatment compared to pre-surgery. Secondary outcomes will include (NRS) or visual
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34 138 analog scale (VAS) score, time to take effect, rescue drug dosage, and quality of life (QoL)
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36 139 using the health questionnaire (SF-36)²¹ at 1 month, 3 months, and 6 months
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39 140 postoperatively, and incidence of adverse events (AEs).

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42 43 44 142 **Information sources and search strategy**

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46 143 A computer-based search strategy will be designed by an experienced librarian and
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49 144 revised by another expert librarian according to the Peer Review of Electronic Search
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52 145 Strategies checklist.²² The primary source of literature will be the following major
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55 146 electronic databases: PubMed/MEDLINE, EMBASE, Web of Science, and the Cochrane
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57 147 Library (from the date of inception until March 15, 2022). The secondary source of
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5 148 potentially relevant research includes conference proceedings for relevant abstracts,
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8 149 clinical trials registers (ClinicalTrials.gov), and the World Health Organization's
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10 150 International Clinical Trial Registry Platform (WHO ICTRP) to identify ongoing studies.
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13 151 The search will encompass a broad range of terms and keywords related to "high-voltage,"
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15 152 "pulsed radiofrequency," "neuropathic pain", and "RCT". The detailed search strategy is
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18 153 presented in **Supplement 2**.

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22 23 155 **Data selection and analysis**

24 25 156 **Study Selection**

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28 157 The Population, Intervention, Comparison, Outcome (PICO) model²³ will be used to
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31 158 determine the specific criteria for selecting studies. Two reviewers (YJ and GF) will
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34 159 independently screen and select the relevant studies. In the initial screening, reviewers
35
36 160 will determine whether the study could be included by screening the titles and abstracts
37
38
39 161 retrieved via database searches. The full texts retained from the initial selection of articles
40
41 162 will be screened to include studies that meet the eligibility criteria. Disagreements
42
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44 163 between the two reviewers will be resolved by a third reviewer (TW). If several studies
45
46 164 present data from the same study population or multiple publications from the same study
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49 165 are published in chronological order, the study with the most direct interventions or the
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52 166 largest sample size will be reserved. The same methods will be used for citation, reference
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54 167 screening, and selection, as well as for protocols registered in clinical trial registries.

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169 **Data extraction**

170 A standardized electronic form for data extraction will be created by ZW. Two reviewers
171 (YJ and GF) will independently extract the following data: study characteristics (e.g.,
172 name of the first author, year of publication, type of study, sample size), population
173 characteristics (e.g., age, gender, disease duration, medical history, preoperative pain
174 intensity, and follow-up period), and outcome data (e.g., primary and secondary outcomes
175 and any AEs caused by PRF treatment). Similarly, a third reviewer will be required to
176 resolve any discrepancies. We will attempt to contact the study authors by email or post
177 for further information in case of any ambiguity or insufficient information.

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179 **Assessment of risk of bias and quality of evidence assessment**

180 Two reviewers (YJ and GF) will independently assess risk of bias (RoB) and
181 discrepancies will be resolved by a third reviewer (ZW). The RoB of RCTs will be
182 assessed according to items in the Cochrane Collaboration's tool.¹⁹

183 We will evaluate the overall quality of a body of evidence in accordance with the Grading
184 of Recommendations Assessment, Development, and Evaluation (GRADE)
185 methodology²⁴ which examines study design, RoB, inconsistency, indirectness, and
186 imprecision. According to the GRADE, quality of evidence will be rated as high,
187 moderate, low, or very low.

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189 **Data synthesis and analysis**

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5 190 Meta-analyses will be conducted using the standard meta-analysis software (RevMan
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8 191 V.5.3, The Nordic Cochrane Center, The Cochrane Collaboration, Copenhagen,
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10 192 Denmark). We will compute standardized mean differences (SMDs) and 95% confidence
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13 193 intervals (CIs) for continuous outcomes, and risk ratios (RR) with 95% CI for binary
14
15 194 outcomes. A two-tailed P value of less than 0.05 is considered statistically significant. We
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18 195 will assess the intervention effects between high-voltage PRF and standard-voltage PRF
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20 196 using pre- to post-intervention changes. When the data in the literature are expressed as
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22
23 197 medians and quartiles, we will use mathematical operations to transform them into mean
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25 198 and standard deviation (SD).^{25 26} We will use forest plots to visualize pooled estimates
26
27
28 199 and the extent of heterogeneity among studies. Heterogeneity will be assessed using the
29
30 200 I^2 statistic. $I^2 > 50\%$ will indicate substantial heterogeneity, and the random-effects model
31
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33 201 will be used to analyze the outcomes; otherwise, a fixed-effect model will be applied.
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36 202 When heterogeneity is found, we will perform subgroup analysis according to
37
38 203 prespecified variables, such as study design, intervention characteristics, or risk of bias.
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40
41 204 The sources of heterogeneity will be explored using sensitivity analysis. A funnel plot²⁷
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43
44 205 or Egger test²⁸ will be used to assess publication bias.
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49 207 **Patient and Public Involvement**

51 208 As our study is a systematic review based on published literature, no patients will be
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54 209 involved in this study.
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211 **Discussion**

212 Several studies have evaluated the efficacy of high voltage PRF in the treatment of NP.
213 Li et al ²⁹ and Wan et al ¹⁷ conducted RCTs and reported that the VAS score declined
214 significantly from the baseline levels in both groups. Moreover, the VAS score in the
215 high-voltage PRF group was significantly lower than that in the standard-voltage PRF
216 group at some time points but not at all follow-up periods. The eight dimensions of the
217 SF-36 scores used to assess QoL between the two groups still require detailed assessment.
218 To date, the incidence of AEs associated with high-voltage PRF and standard-voltage
219 PRF group is not clear. Therefore, it is important for physicians to accumulate more high-
220 level evidence regarding the efficacy and safety of different PRF output voltages for NP
221 patients' therapy.

222 The objective of our study is to compare the efficacy and safety of high-voltage PRF and
223 standard-voltage PRF for NP therapy and provide clinical evidence for the choice of PRF
224 modes in clinical practice via synthesizing the existing literature. However, this study has
225 some limitations. The sample size of the eligible RCTs was not large and the accuracy of
226 the conclusions of our research may be biased due to language limitations, as we will only
227 include studies published in English. Overall, the study findings will provide
228 comprehensive information for future study designs in terms of interventional treatment
229 of NP.

230 **Abbreviations**

231 PRF, Pulsed radiofrequency; NP, neuropathic pain; RCTs, randomized controlled trials;

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5 232 NRS, numeric rating scale; VAS, visual analog scale; QoL, quality of life; AEs, adverse
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8 233 events; RoB, risk of bias; GRADE, Grading of Recommendations Assessment,
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10 234 Development, and Evaluation; SMDs, standardized mean differences; CIs, confidence
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13 235 intervals; RR, risk ratios.

236 **Ethics and dissemination**

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18 237 Ethical approval was waived as our systematic review will be based on published
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21 238 literature. The results of this study will be submitted to a peer-reviewed journal.

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240 **Acknowledgments** The authors would like to thank the participants of the study for their cooperation.

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26 241
26 242 **Contributors** YJ, ZW, TW and TW made substantial contributions to clinical study design; YJ, YM
27
28 243 and GF made substantial contributions to manuscript preparation, editing and review; KF made
29
30 244 contributions to English language editing; YM, KF and GF consulted about clinical issues; YJ, YM,
31
32 245 TW and TW have given final approval of the version to be published. YJ, ZW and YM contributed
33
34 246 equally to this work. TW is responsible as corresponding author.

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36 247
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36
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251 **Consent for publication** All authors consented.

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253 **Conflicts of interest** None.

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2021;12:746035. doi: 10.3389/fneur.2021.746035 [published Online First: 2021/10/29]

For peer review only

Supplement 1. PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No	Checklist item	Check results
ADMINISTRATIVE INFORMATION			
Title:			
Identification	1a	Identify the report as a protocol of a systematic review	Yes
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	Yes
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	Yes
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	Yes
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	Yes
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	Yes
Support:			
Sources	5a	Indicate sources of financial or other support for the review	Yes
Sponsor	5b	Provide name for the review funder and/or sponsor	Yes
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	Yes

INTRODUCTION

Rationale	6	Describe the rationale for the review in the context of what is already known	Yes
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	Yes

METHODS

Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	Yes
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	Yes
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	Yes

Study records:

Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	Yes
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	Yes
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	Yes
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	Yes
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	Yes

Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	Yes
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesized	Yes
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2 , Kendall's τ)	Yes
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	Yes
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	Yes
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	Yes
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	Yes

*** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

From: Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart L, PRISMA-P Group. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ. 2015 Jan 2;349(jan02 1):g7647.

Search step	Search terms
#1	<p>"neuralgia"[MeSH Terms] OR ("neuralgia"[MeSH Terms] OR "neuralgia"[All Fields] OR "neuralgias"[All Fields]) OR ("neuralgia"[MeSH Terms] OR "neuralgia"[All Fields] OR ("neuropathic"[All Fields] AND "pain"[All Fields]) OR "neuropathic pain"[All Fields]) OR ("neuralgia"[MeSH Terms] OR "neuralgia"[All Fields] OR ("neuropathic"[All Fields] AND "pains"[All Fields]) OR "neuropathic pains"[All Fields]) OR ("neuralgia"[MeSH Terms] OR "neuralgia"[All Fields] OR ("pain"[All Fields] AND "neuropathic"[All Fields]) OR "pain neuropathic"[All Fields]) OR ("neuralgia"[MeSH Terms] OR "neuralgia"[All Fields] OR ("pains"[All Fields] AND "neuropathic"[All Fields]) OR "pains neuropathic"[All Fields]) OR ("neuralgia"[MeSH Terms] OR "neuralgia"[All Fields] OR "neurodynia"[All Fields]) OR ("neuralgia"[MeSH Terms] OR "neuralgia"[All Fields]) OR ("neuralgia"[MeSH Terms] OR "neuralgia"[All Fields] OR ("neuralgia"[All Fields] AND "atypical"[All Fields]) OR "neuralgia atypical"[All Fields]) OR ("neuralgia"[MeSH Terms] OR "neuralgia"[All Fields] OR ("atypical"[All Fields] AND "neuralgia"[All Fields]) OR "atypical neuralgia"[All Fields]) OR ("neuralgia"[MeSH Terms] OR "neuralgia"[All Fields] OR ("atypical"[All Fields] AND "neuralgias"[All Fields]) OR "atypical neuralgias"[All Fields]) OR ("neuralgia"[MeSH Terms] OR "neuralgia"[All Fields] OR ("neuralgias"[All Fields] AND "atypical"[All Fields]) OR "neuralgias atypical"[All Fields]) OR ("neuralgia"[MeSH Terms] OR "neuralgia"[All Fields] OR ("neuralgia"[All Fields] AND "iliohypogastric"[All Fields] AND "nerve"[All Fields])) OR ("neuralgia"[MeSH Terms] OR "neuralgia"[All Fields] OR ("iliohypogastric"[All Fields] AND "nerve"[All Fields] AND "neuralgia"[All Fields])) OR ("neuralgia"[MeSH Terms] OR "neuralgia"[All Fields] OR ("iliohypogastric"[All Fields] AND "nerve"[All Fields] AND "neuralgias"[All Fields])) OR ("neuralgia"[MeSH Terms] OR "neuralgia"[All Fields] OR ("nerve"[All Fields] AND "neuralgia"[All Fields] AND "iliohypogastric"[All Fields])) OR ("neuralgia"[MeSH Terms] OR "neuralgia"[All Fields] OR ("nerve"[All Fields] AND "neuralgias"[All Fields] AND "iliohypogastric"[All Fields])) OR ("neuralgia"[MeSH Terms] OR "neuralgia"[All Fields] OR ("neuralgias"[All Fields] AND "iliohypogastric"[All Fields] AND "nerve"[All Fields])) OR ("neuralgia"[MeSH Terms] OR "neuralgia"[All Fields] OR ("paroxysmal"[All Fields] AND "nerve"[All Fields] AND "pain"[All Fields]) OR "paroxysmal nerve pain"[All Fields]) OR ("neuralgia"[MeSH Terms] OR "neuralgia"[All Fields] OR ("nerve"[All Fields] AND "pain"[All Fields] AND "paroxysmal"[All Fields])) OR ("neuralgia"[MeSH Terms] OR "neuralgia"[All Fields] OR ("nerve"[All Fields] AND "pains"[All Fields] AND "paroxysmal"[All Fields])) OR ("neuralgia"[MeSH Terms] OR "neuralgia"[All Fields] OR ("pain"[All Fields] AND "paroxysmal"[All Fields] AND "nerve"[All Fields])) OR ("neuralgia"[MeSH Terms] OR "neuralgia"[All Fields] OR ("pains"[All Fields] AND "paroxysmal"[All Fields] AND "nerve"[All Fields])) OR</p>

("neuralgia"[MeSH Terms] OR "neuralgia"[All Fields] OR ("paroxysmal"[All Fields] AND "nerve"[All Fields] AND "pains"[All Fields])) OR
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 "supraorbital neuralgia"[All Fields]) OR ("neuralgia"[MeSH Terms] OR "neuralgia"[All Fields] OR ("supraorbital"[All Fields] AND "neuralgias"[All Fields])) OR ("neuralgia"[MeSH Terms] OR "neuralgia"[All Fields] OR
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	Terms] OR "neuralgia"[All Fields] OR ("neuralgias"[All Fields] AND "ilioinguinal"[All Fields]))
#2	"pulsed radiofrequency treatment"[MeSH Terms] OR "pulsed radiofrequency treatments"[All Fields] OR (("radiofrequencies"[All Fields] OR "Radiofrequency"[All Fields] OR "radiofrequent"[All Fields]) AND "treatment pulsed"[All Fields]) OR (("radiofrequencies"[All Fields] OR "Radiofrequency"[All Fields] OR "radiofrequent"[All Fields]) AND "treatments pulsed"[All Fields]) OR "treatment pulsed radiofrequency"[All Fields] OR "treatments pulsed radiofrequency"[All Fields] OR "pulsed radio frequency treatment"[All Fields]
#3	(clinical[tiab] AND trial[tiab]) OR "clinical trials as topic"[mesh] OR "clinical trial"[pt] OR random*[tiab] OR "random allocation"[mesh] OR "therapeutic use"[sh]
#4	#1 AND #2 AND #3

BMJ Open

Efficacy and safety of high-voltage pulsed radiofrequency ablation versus standard-voltage pulsed radiofrequency ablation for patients with neuropathic pain: protocol for a systematic review and meta-analysis

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2022-063385.R1
Article Type:	Protocol
Date Submitted by the Author:	24-May-2022
Complete List of Authors:	Jia, Yitong; Xuanwu Hospital Capital Medical University, Anesthesiology wang, zheng; Xuanwu Hospital Capital Medical University, Department of General Surgery Ma, Yanhui; Xuanwu Hospital Capital Medical University, Anesthesiology Wang, Tengting; Xuanwu Hospital Capital Medical University, Thoracic Surgery Feng, Kunpeng; Xuanwu Hospital Capital Medical University, Anesthesiology Feng, Guang; Xuanwu Hospital Capital Medical University, Anesthesiology Wang, Tianlong; Xuanwu Hospital Capital Medical University
Primary Subject Heading:	Anaesthesia
Secondary Subject Heading:	Neurology
Keywords:	PAIN MANAGEMENT, Neurological pain < NEUROLOGY, Pain management < ANAESTHETICS

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Manuscripts

1 **Efficacy and safety of high-voltage pulsed**
2 **radiofrequency ablation versus standard-voltage**
3 **pulsed radiofrequency ablation for patients with**
4 **neuropathic pain: protocol for a systematic review and**
5 **meta-analysis**

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21 Yitong Jia, Zheng Wang and Yanhui Ma contributed equally to this paper.

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78 **Abstract**
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10 **Introduction** Pulsed radiofrequency (PRF) ablation is commonly used for the treatment
11 of neuropathic pain (NP). However, it is unclear whether increasing the output voltage of
12 PRF can safely improve its efficacy. This study aims to compare the efficacy and safety
13 of high-voltage PRF ablation and standard-voltage PRF ablation for the treatment of
14 patients with NP.
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17 **Methods and analysis** We will search PubMed/MEDLINE, EMBASE, Web of Science,
18 the Cochrane Library, conference proceedings for relevant abstracts, clinical trials
19 registers (ClinicalTrials.gov), and the World Health Organization's International Clinical
20 Trial Registry Platform (WHO ICTRP) (from the date of inception until March 15, 2022).
21 Only randomized controlled trials (RCTs) will be included. Two reviewers (YJ and GF)
22 will independently perform study screening and selection, data extraction, risk of bias
23 assessment, and quality of evidence assessment. The primary outcome of this meta-
24 analysis will be the efficiency rate in patients with NP. The secondary outcomes will
25 include numeric rating scale score, visual analog scale score, time to take effect, rescue
26 drug dosage, quality of life using the health questionnaire (SF-36), and the incidence of
27 adverse events. Meta-analyses will be conducted using standard meta-analysis software
28 (RevMan V.5.3, The Nordic Cochrane Center, The Cochrane Collaboration, Copenhagen,
29 Denmark).
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36 **Ethics and dissemination** The requirement for ethical approval was waived as our
37 systematic review will be based on published literature. The results of this study will be
38 submitted to a peer-reviewed journal.
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43 **PROSPERO registration number** CRD42022297804.
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47 **Strengths and limitations of this study**

48 To the best of our knowledge, this will be the first systematic review and meta-analysis
49 to evaluate the efficacy and safety of high-voltage PRF ablation for the treatment of
50 patients with NP. To provide unbiased information, only RCTs will be included.

51 The study findings will provide comprehensive information for future study designs in
52 terms of interventional treatment of neuropathic pain.

53 The accuracy of our research conclusions might be subjected to language limitations as
54 only studies published in English will be included.
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58 **Key words:** high-voltage, pulsed radiofrequency, neuropathic pain, randomized
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4 63 controlled trials
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9 65 **Introduction**

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11 66 Neuropathic pain (NP) is a common chronic pain condition caused by lesions or diseases
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14 67 affecting the somatosensory nervous system, including trigeminal neuralgia, peripheral
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17 68 nerve injury pain, painful polyneuropathy, post herpetic neuralgia, and central post stroke
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20 69 pain.¹ Epidemiological data have reported that the global prevalence of NP is
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22 70 approximately 6.9% - 10%.² Neuropathic pain is a refractory pain syndrome with a long
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25 71 duration of occurrence, frequent recurrent attacks, and poor response to traditional
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28 72 analgesics. Most patients with NP suffer from ongoing or intermittent spontaneous pain
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31 73 accompanied by burning, pricking, and squeezing sensations, and have a poor quality of
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34 74 life (QoL).³ Therefore, finding an effective treatment option for NP and improving
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36 75 patients' QoL is of great importance.

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38 76 In recent years, pulsed radiofrequency (PRF) ablation, a new type of neuromodulation
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41 77 technique, has been successfully applied in the treatment of NP.⁴⁻⁹ Different from
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43
44 78 continuous radiofrequency (CRF), which produces heat by friction and vibration, leading
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47 79 to thermocoagulation, denaturation, and necrosis of the target tissue^{10 11}, PRF provides
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50 80 pulsed energy waves followed by a 480-ms heat dissipation interval, and the temperature
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53 81 does not exceed 42°C.¹²⁻¹⁴ PRF treatment exerts its effect via the modulation of nerve
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56 82 function , which is a result of the electric field effect and not the impedance of pain
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59 83 signal transduction;^{15 16} thus, PRF ablation is a nondestructive technique that can be
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62 84 repeatedly applied without causing nerve tissue damage.

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5 85 The standard proposed PRF parameters are set as follows: an output voltage of 45 V,
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8 86 temperature of 42°C, pulse frequency of 2 Hz, output frequency of 500 kHz, continuous
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11 87 current action of 20 ms, and intermission period of 480 ms. Recently, scholars have
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13 88 attempted to treat patients with NP using high-voltage PRF ablation. Teixeira and Sluijter
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15 89 first reported that a high-voltage PRF ablation of 60 V used to treat patients with
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18 90 discogenic pain attained satisfactory efficacy that lasted over 3 months.¹⁷ In 2013, Luo et
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21 91 al found that the postoperative numeric rating scale (NRS) score had a significant negative
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23 92 correlation with the output voltage of PRF.¹⁸ Afterwards, Luo et al compared the efficacy
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26 93 of high-voltage PRF with standard-voltage PRF for idiopathic trigeminal neuralgia (TN)
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29 94 patients who responded poorly to oral carbamazepine or nerve blockade by steroid, and
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31 95 the results revealed the 1- year effective rate of high-voltage PRF (69%) was significantly
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34 96 higher than that in the standard-voltage PRF treatment(19%) (P = 0.000).¹⁹ Additionally,
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37 97 they compared the efficacy of high voltage PRF and standard voltage PRF for refractory
38
39 98 neuralgia infraorbital nerve therapy, and reported that high voltage PRF ablation could
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42 99 achieve higher response rates at 1 month, 3 months, 6 months, and 1 year post-
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44 100 procedure.²⁰ Jia et al retrospectively analyzed the medical data of patients with idiopathic
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47 101 TN undergoing PRF. The study found that for patients who did not respond to the first
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50 102 PRF treatment and underwent the second PRF treatment, a higher dose of out-put voltage
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52 103 than the initial one could achieve improved analgesic effect²¹⁻²³.
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55 104 However, the number of patients who experienced mild numbness postoperatively was
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57 105 greater in the high-voltage group (27%) than in the standard-voltage group (13%).²⁰ In
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5 106 addition, a randomized controlled trial (RCT) conducted by Wan et al showed that the
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8 107 scores were significantly lower in the high-voltage group than in the standard-voltage
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11 108 group at 3 and 6 months; however, no significant difference was observed at 1 month
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13 109 after treatment.²⁴ A study by Wan et al revealed that the incidence of ecchymoses in the
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15 110 high-voltage group (19.2%) was higher than that in the standard-voltage group (12.1%).
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18 111 As a result, further analysis is required to determine whether the efficacy of high-voltage
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21 112 PRF ablation at different time points is superior to that of standard-voltage PRF ablation,
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23 113 and whether high-voltage PRF ablation is a safe treatment method for NP.
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26 114 The primary objectives of this study will be to compare the efficacy and safety of high-
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29 115 voltage PRF ablation and standard-voltage PRF ablation for the treatment of NP at
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31 116 different time points postoperatively through a systematic review and meta-analysis of
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34 117 RCTs.

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119 **Methods**

120 This protocol was developed according to the reporting guidelines of Preferred Reporting
121
122 121 Items for Systematic Reviews and Meta-Analyses Protocols (PRISMA-P) statement²⁵
123
124 122 **(checklist in Supplement 1)**. The protocol for this systematic review was registered in
125
126 123 the PROSPERO database (registration number: CRD42022297804). Our systematic
127
128
129 124 review will be conducted in accordance with the recommendations of the Cochrane
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131
132 125 Handbook for Systematic Reviews of Interventions.²⁶ Any amendments made to this
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135 126 protocol and the whole review process will be updated in a timely manner on the

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5 127 PROSPERO registration and the final manuscript.
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10 129 **Criteria for considering eligible studies**

11 12 13 130 **Types of studies**

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15 131 Only RCTs will be included. All studies must be published in English. Experimental
16
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18 132 animal studies will be excluded.
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22 23 134 **Participants**

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25 135 Patients with NP conditions recognized and defined by the International Association for
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28 136 the Study of Pain (IASP)²⁷ will be included. Neuropathic pain is initiated or caused by a
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31 137 primary lesion or dysfunction of the nervous system. Studies regarding diabetic
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34 138 neuropathy, complex regional pain syndrome type I, low back pain without radicular pain,
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36 139 and postsurgical pain will be excluded.
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41 141 **Interventions and Comparators**

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44 142 We will examine trials investigating high-voltage PRF treatment for patients with NP.
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47 143 The high-voltage PRF treatment will be set to the manual pulse mode: the initial voltage
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50 144 will be 40 or 45 V, and the output voltage will then be gradually increased to the highest
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52 145 voltage the patient can tolerate (temperature control below 50°C). The comparator will
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54 146 be the standard PRF treatment.
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148 **Outcome measures**

149 The primary outcome of this meta-analysis is the efficiency rate in patients with NP. The
150 predefined time points for the efficiency rate will be 1 month, 3 months, and 6 months
151 after the procedure. Additionally, 1-year or 2-year time point will also be considered.
152 Treatment efficiency recurrence is defined as a pain reduction of greater than 50% after
153 treatment compared to pre-surgery. Secondary outcomes will include (NRS) or visual
154 analog scale (VAS) score, time to take effect, rescue drug dosage, quality of life (QoL)
155 determined using a health questionnaire (SF-36)²⁸ at 1 month, 3 months, and 6 months
156 postoperatively, and incidence of adverse events (AEs).

158 **Information sources and search strategy**

159 A computer-based search strategy will be designed by an experienced librarian and
160 revised by another expert librarian according to the Peer Review of Electronic Search
161 Strategies checklist.²⁹ The primary source of literature will be the following major
162 electronic databases: PubMed/MEDLINE, EMBASE, Web of Science, and the Cochrane
163 Library (from the date of inception until March 15, 2022). The secondary source of
164 potentially relevant research includes conference proceedings for relevant abstracts,
165 clinical trials registers (ClinicalTrials.gov), and the World Health Organization's
166 International Clinical Trial Registry Platform (WHO ICTRP) to identify ongoing studies.
167 The search will encompass a broad range of terms and keywords related to "high-voltage,"
168 "pulsed radiofrequency," "neuropathic pain," and "RCT". The detailed search strategy is

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5 169 presented in **Supplement 2**.

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10 171 **Data selection and analysis**

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13 172 **Study Selection**

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15 173 We will use the Population, Intervention, Comparison, Outcome (PICO) model³⁰to

16
17 174 determine the specific criteria for selecting studies. Two reviewers (YJ and GF) will

18
19 175 independently screen and select the relevant studies. During the initial screening,

20
21 176 reviewers will determine whether the study could be included by screening the titles and

22
23 177 abstracts retrieved via database search. We will screen the full texts retained from the

24
25 178 initial selection of articles to include studies that meet the eligibility criteria.

26
27 179 Disagreements between the two reviewers will be resolved by a third reviewer (TW). If

28
29 180 several studies present data from the same study population or multiple publications from

30
31 181 the same study are published in chronological order, the study with the most direct

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33 182 interventions or the largest sample size will be selected. The same methods will be used

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35 183 for citation, reference screening, and selection, as well as for protocols registered in

36
37 184 clinical trial registries.

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42 186 **Data extraction**

43
44 187 A standardized electronic form for data extraction will be created by ZW. Two reviewers

45
46 188 (YJ and GF) will independently extract the following data: study characteristics (e.g.,

47
48 189 name of the first author, year of publication, type of study, sample size), population

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5 190 characteristics (e.g., age, gender, disease duration, medical history, preoperative pain
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8 191 intensity, and follow-up period), and outcome data (e.g., primary and secondary outcomes
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10 192 and any AEs caused by PRF treatment). Similarly, a third reviewer will be required to
11
12
13 193 resolve any discrepancies. We will attempt to contact the study authors by email or post
14
15 194 for further information in case of any ambiguity or insufficient information. Table 1
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17
18 195 presents the characteristics of the studies that will be included.
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21 196

197 **Assessment of risk of bias and quality of evidence assessment**

25 198 Two reviewers (YJ and GF) will independently assess the risk of bias (RoB) and a third
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27
28 199 reviewer (ZW) will resolve discrepancies. The RoB of RCTs will be assessed according
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31 200 to items in the Cochrane Collaboration's tool.²⁶
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34 201 We will evaluate the overall quality of the body of evidence in accordance with the
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36 202 Grading of Recommendations Assessment, Development, and Evaluation (GRADE)
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39 203 methodology,³¹ which examines study design, RoB, inconsistency, indirectness, and
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41 204 imprecision. Accordingly, quality of evidence will be rated as high, moderate, low, or
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44 205 very low.
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207 **Data synthesis and analysis**

51 208 Meta-analyses will be conducted using the standard meta-analysis software (RevMan
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54 209 V.5.3, The Nordic Cochrane Center, The Cochrane Collaboration, Copenhagen,
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57 210 Denmark). We will compute standardized mean differences (SMDs) and 95% confidence
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5 211 intervals (CIs) for continuous outcomes, and risk ratios (RR) with 95% CI for binary
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8 212 outcomes. A two-tailed p-value < 0.05 will be considered statistically significant. We will
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10 213 assess the intervention effects between high-voltage PRF and standard-voltage PRF using
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13 214 pre- to post-intervention changes. When the data in the literature are expressed as median
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15 215 values and quartiles, we will use mathematical operations to transform them into mean
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18 216 and standard deviation (SD).^{32 33} Additionally, we will use forest plots to visualize pooled
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21 217 estimates and the extent of heterogeneity among studies. Heterogeneity will be assessed
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23 218 using the I² statistic. I² > 50% is an indication of substantial heterogeneity, and in such
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26 219 cases the random-effects model will be used to analyze the outcomes; otherwise, a fixed-
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29 220 effect model will be applied. If heterogeneity is observed, we will perform subgroup
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31 221 analysis according to prespecified variables, such as study design, intervention
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33 222 characteristics, or RoB. The sources of heterogeneity will be explored using sensitivity
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36 223 analysis. A funnel plot³⁴ or Egger test³⁵ will be used to assess publication bias.
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40 41 225 **Patient and Public Involvement**

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44 226 Since our study is a systematic review based on published literature, no patients will be
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47 227 involved.
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50 51 52 53 229 **Discussion**

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57 230 Our study aims to compare the efficacy and safety of high-voltage PRF ablation and
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5 231 standard-voltage PRF ablation for NP therapy and provide clinical evidence for the
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8 232 selection of PRF modes in clinical practice via synthesizing RCTs in journal publications.
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10 233 This study has some limitations. The sample size of the eligible RCTs might not be large
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13 234 and the accuracy of our research conclusions might be biased due to language limitations,
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15 235 as we will only include studies published in English. Overall, the study findings will
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18 236 provide comprehensive information for future study designs in terms of interventional
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21 237 treatment of NP.

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27 **Abbreviations**

28 240 PRF, Pulsed radiofrequency; NP, neuropathic pain; RCTs, randomized controlled trials;
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31 241 NRS, numeric rating scale; VAS, visual analog scale; QoL, quality of life; AEs, adverse
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34 242 events; RoB, risk of bias; GRADE, Grading of Recommendations Assessment,
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36 243 Development, and Evaluation; SMDs, standardized mean differences; CIs, confidence
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39 244 intervals; RR, risk ratios.

40 **Ethics and dissemination**

41 245 Ethical approval was waived as our systematic review will be based on published
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44 246 literature. The results of this study will be submitted to a peer-reviewed journal.
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51 250

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53
54 252 and GF made substantial contributions to manuscript preparation, editing and review; KF made
55
56 253 contributions to English language editing; YM, KF and GF consulted about clinical issues; YJ, YM,
57
58 254 TW and TW have given final approval of the version to be published. YJ, ZW and YM contributed
59
60 255 equally to this work. TW is responsible as corresponding author.
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13 260 **Consent for publication** All authors consented.
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18 262 **Conflicts of interest** None.
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383 Table 1 Main characteristics of RCTs comparing the efficacy and safety of high-voltage PRF and standard-voltage PRF for the treatment of NP

Study ID	Sample size	Types of neuropathic pain	Setting	Duration	Number of female (%) / male (%) patients	Age (years)	Preoperative pain (VAS/ NRS)	Preoperative QoL	Postoperative pain (VAS/ NRS)	Postoperative QoL	Complications
A											
B											
C											
.....											

384 Abbreviations: RCT, randomized controlled trials; VAS: visual analog scale; NRS: numeric rating scale; QoL: quality of life.

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Supplement 1. PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No	Checklist item	Page No
ADMINISTRATIVE INFORMATION			
Title:			
Identification	1a	Identify the report as a protocol of a systematic review	1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	n/a
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	2
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	11
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	n/a
Support:			
Sources	5a	Indicate sources of financial or other support for the review	11
Sponsor	5b	Provide name for the review funder and/or sponsor	11
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	11

INTRODUCTION

Rationale	6	Describe the rationale for the review in the context of what is already known	3
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	3-4

METHODS

Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	5
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	6-7
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	6-7

Study records:

Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	7
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	7
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	7
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	9
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	6

Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	8
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesized	9
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2 , Kendall's τ)	9
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	9
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	9
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	8
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	8

*** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

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Search step	Search terms
#1	<p>"neuralgia"[MeSH Terms] OR ("neuralgia"[MeSH Terms] OR "neuralgia"[All Fields] OR "neuralgias"[All Fields]) OR ("neuralgia"[MeSH Terms] OR "neuralgia"[All Fields] OR ("neuropathic"[All Fields] AND "pain"[All Fields]) OR "neuropathic pain"[All Fields]) OR ("neuralgia"[MeSH Terms] OR "neuralgia"[All Fields] OR ("neuropathic"[All Fields] AND "pains"[All Fields]) OR "neuropathic pains"[All Fields]) OR ("neuralgia"[MeSH Terms] OR "neuralgia"[All Fields] OR ("pain"[All Fields] AND "neuropathic"[All Fields]) OR "pain neuropathic"[All Fields]) OR ("neuralgia"[MeSH Terms] OR "neuralgia"[All Fields] OR ("pains"[All Fields] AND "neuropathic"[All Fields]) OR "pains neuropathic"[All Fields]) OR ("neuralgia"[MeSH Terms] OR "neuralgia"[All Fields] OR "neurodynia"[All Fields]) OR ("neuralgia"[MeSH Terms] OR "neuralgia"[All Fields]) OR ("neuralgia"[MeSH Terms] OR "neuralgia"[All Fields] OR ("neuralgia"[All Fields] AND "atypical"[All Fields]) OR "neuralgia atypical"[All Fields]) OR ("neuralgia"[MeSH Terms] OR "neuralgia"[All Fields] OR ("atypical"[All Fields] AND "neuralgia"[All Fields]) OR "atypical neuralgia"[All Fields]) OR ("neuralgia"[MeSH Terms] OR "neuralgia"[All Fields] OR ("atypical"[All Fields] AND "neuralgias"[All Fields]) OR "atypical neuralgias"[All Fields]) OR ("neuralgia"[MeSH Terms] OR "neuralgia"[All Fields] OR ("neuralgias"[All Fields] AND "atypical"[All Fields]) OR "neuralgias atypical"[All Fields]) OR ("neuralgia"[MeSH Terms] OR "neuralgia"[All Fields] OR ("neuralgia"[All Fields] AND "iliohypogastric"[All Fields] AND "nerve"[All Fields])) OR ("neuralgia"[MeSH Terms] OR "neuralgia"[All Fields] OR ("iliohypogastric"[All Fields] AND "nerve"[All Fields] AND "neuralgia"[All Fields])) OR ("neuralgia"[MeSH Terms] OR "neuralgia"[All Fields] OR ("iliohypogastric"[All Fields] AND "nerve"[All Fields] AND "neuralgias"[All Fields])) OR ("neuralgia"[MeSH Terms] OR "neuralgia"[All Fields] OR ("nerve"[All Fields] AND "neuralgia"[All Fields] AND "iliohypogastric"[All Fields])) OR ("neuralgia"[MeSH Terms] OR "neuralgia"[All Fields] OR ("nerve"[All Fields] AND "neuralgias"[All Fields] AND "iliohypogastric"[All Fields])) OR ("neuralgia"[MeSH Terms] OR "neuralgia"[All Fields] OR ("neuralgias"[All Fields] AND "iliohypogastric"[All Fields] AND "nerve"[All Fields])) OR ("neuralgia"[MeSH Terms] OR "neuralgia"[All Fields] OR ("paroxysmal"[All Fields] AND "nerve"[All Fields] AND "pain"[All Fields]) OR "paroxysmal nerve pain"[All Fields]) OR ("neuralgia"[MeSH Terms] OR "neuralgia"[All Fields] OR ("nerve"[All Fields] AND "pain"[All Fields] AND "paroxysmal"[All Fields])) OR ("neuralgia"[MeSH Terms] OR "neuralgia"[All Fields] OR ("nerve"[All Fields] AND "pains"[All Fields] AND "paroxysmal"[All Fields])) OR ("neuralgia"[MeSH Terms] OR "neuralgia"[All Fields] OR ("pain"[All Fields] AND "paroxysmal"[All Fields] AND "nerve"[All Fields])) OR ("neuralgia"[MeSH Terms] OR "neuralgia"[All Fields] OR ("pains"[All Fields] AND "paroxysmal"[All Fields] AND "nerve"[All Fields])) OR</p>

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 ("neuralgia"[All Fields] AND "vidian"[All Fields]) OR "neuralgia vidian"[All Fields]) OR ("neuralgia"[MeSH Terms] OR "neuralgia"[All Fields] OR
 ("neuralgias"[All Fields] AND "vidian"[All Fields])) OR ("neuralgia"[MeSH Terms] OR "neuralgia"[All Fields] OR ("vidian"[All Fields] AND
 "neuralgia"[All Fields])) OR ("neuralgia"[MeSH Terms] OR "neuralgia"[All Fields] OR ("vidian"[All Fields] AND "neuralgias"[All Fields])) OR
 ("neuralgia"[MeSH Terms] OR "neuralgia"[All Fields] OR ("nerve"[All Fields] AND "pain"[All Fields]) OR "nerve pain"[All Fields]) OR ("neuralgia"[MeSH Terms] OR "neuralgia"[All Fields] OR ("nerve"[All Fields] AND "pains"[All Fields]) OR "nerve pains"[All Fields]) OR ("neuralgia"[MeSH Terms] OR
 "neuralgia"[All Fields] OR ("pain"[All Fields] AND "nerve"[All Fields]) OR "pain nerve"[All Fields]) OR ("neuralgia"[MeSH Terms] OR "neuralgia"[All Fields] OR ("pains"[All Fields] AND "nerve"[All Fields])) OR
 ("neuralgia"[MeSH Terms] OR "neuralgia"[All Fields] OR ("neuralgia"[All Fields] AND "ilioinguinal"[All Fields])) OR ("neuralgia"[MeSH Terms] OR "neuralgia"[All Fields] OR ("ilioinguinal"[All Fields] AND "neuralgia"[All Fields]) OR "ilioinguinal neuralgia"[All Fields]) OR ("neuralgia"[MeSH Terms] OR
 "neuralgia"[All Fields] OR ("ilioinguinal"[All Fields] AND "neuralgias"[All Fields]) OR "ilioinguinal neuralgias"[All Fields]) OR ("neuralgia"[MeSH

	Terms] OR "neuralgia"[All Fields] OR ("neuralgias"[All Fields] AND "ilioinguinal"[All Fields]))
#2	"pulsed radiofrequency treatment"[MeSH Terms] OR "pulsed radiofrequency treatments"[All Fields] OR (("radiofrequencies"[All Fields] OR "Radiofrequency"[All Fields] OR "radiofrequent"[All Fields]) AND "treatment pulsed"[All Fields]) OR (("radiofrequencies"[All Fields] OR "Radiofrequency"[All Fields] OR "radiofrequent"[All Fields]) AND "treatments pulsed"[All Fields]) OR "treatment pulsed radiofrequency"[All Fields] OR "treatments pulsed radiofrequency"[All Fields] OR "pulsed radio frequency treatment"[All Fields]
#3	(clinical[tiab] AND trial[tiab]) OR "clinical trials as topic"[mesh] OR "clinical trial"[pt] OR random*[tiab] OR "random allocation"[mesh] OR "therapeutic use"[sh]
#4	#1 AND #2 AND #3